

### **REMARKS**

Claims 1, 3-11, 15, 16, 18-26 and 69 remain before the Examiner for reconsideration. Claims 12-14, 17, 27-68, and 70-103 have been withdrawn. Claim 2 has previously been canceled without prejudice. Claims 71-103 are canceled without prejudice. New claims 104-112 have been added.

In the Office Action dated January 16, 2009 the Examiner withdrew claim 12 asserting that:

Claim 12 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 08/15/2006 to elect an aliphatic multifunctional isocyanate precursor. Since applicants have amended claim 12 to recite an amino acid based isocyanate precursor the claim is now drawn to an unelected species.

The Examiner rejected claims 1,3,7-8,10-11,19-22,27,34-35 and 69 under 35U.S.C. 102(b) "as being anticipated by Lipatova et al. (Macromol. Symp. 152,139-150 (2000)), for the reasons set forth in the previous office action filed 11/30/2007."

The Examiner also rejected Claims 1,3-11,15-16,18-20,22,25 and 69 under 35 U.S.C. 102(e) "as being anticipated by Beckman et al. (US 7,264,823 B2), for the reasons set forth in the previous office action filed 11/30/2007."

The Examiner rejected claims 1,3-4,7-8,12,19,22,27-30,33 and 69 under 35 U.S.C. 102(e) "as being anticipated by Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the previous office action filed 11/30/2007".

The Examiner further rejected claims 1,3-11,15-16,18-26 and 69 under 35 U.S.C. 103(a) "as being unpatentable over Zhang et al. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et al. (US 6,221,997 B1), for the reasons set forth in the previous office action filed 11/30/2007".

In response to the Applicants' argument set forth in the Amendment filed:

Applicant's arguments filed 11/03/2008 have been fully considered but they are not persuasive.

Applicants assert that none of the references above describe reacting a multifunctional isocyanate with a bioactive agent in water. Applicants assert that water exerts an effect on the reaction in that it acts as a chain extender; therefore the examiner cannot ignore the limitation as this leads to a patentable distinction.

The relevance of this assertion is unclear. Firstly applicant's product shown at the top of page 21 in the second scheme from the top is incorrect, it should be a polyurethane, (note the oxygen between the carbonyl carbon and the nitrogen -RH<sub>2</sub>COONHR-). Even if applicants are correct in that water acts as a chain extender for the reaction (something which is not recited within claims 1 or 69) the polyurethane produced is still the same as those described in the references above. Water does not change the chemical structure of the product; it is still a polyurethane that is the same as the polyurethanes described in the references cited above. All that claims 1 and 69 as currently amended require is a polyurethane composition formed from the reaction of an isocyanate and a bioactive agent. Since the references alone or in combination are within the scope of applicants claimed polyurethane composition the rejections stand. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Furthermore applicants note at paragraph [0008] within their own specification that Zhang and coworkers used water as chain extenders for the prepolymers. Also Beckman describes using water in reactions of LDI and glucose to make a foamed material. See col 8 lin 21- 55. Furthermore as stated throughout Beckman a mixture of molecules that includes a multi-isocyanate functional groups and a multi functional precursor molecule form a crosslinked polymer network upon contact with organic tissue in the presence of water. See previous office actions and abstract of Beckman.

Applicants also assert that it is not clear from Liptova if HDI was combined with Heparin.

The examiner respectfully disagrees. Clearly the use of HDI as a diisocyanate is described within the section of the paper discussing hemocompatible segmented polyurethanes containing heparin fragments.

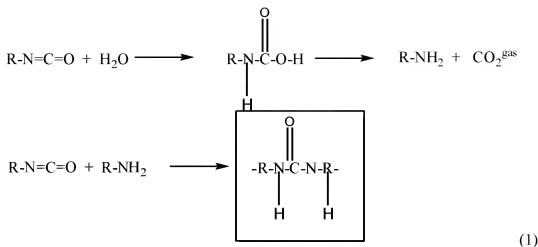
Applicants respectfully traverse the Examiner's rejections and will address each rejection individually.

### **Section 102**

**Claims 1,3,7-8,10-11,19-22,27,34-35 and 69 are not anticipated under 35U.S.C. 102(b) by Liptova et al.**

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The Examiner is correct that "the product shown at the top of page 21 [of the Amendment filed November 3, 2008] in the second scheme from the top is incorrect." The reaction of an isocyanate with water to form a urea repeat unit is more correctly set forth as equation (1) below:



See, for example, Odian, G.G., Principles of Polymerization, Fourth Edition, Wiley Interscience, pp 130 (2004).

However, the Examiner's assertion that:

Even if applicants are correct in that water acts as a chain extender for the reaction (something which is not recited within claims 1 or 69) the polyurethane produced is still the same as those described in the references above. Water does not change the chemical structure of the product; it is still a polyurethane that is the same as the polyurethanes described in the references cited above.

is clearly and demonstrably erroneous. The Examiner is correct that the claims of the present invention are drawn to a "polyurethane" composition, but polyurethane compositions differ widely in their chemical structure or composition. As known to those skilled in the art, isocyanates are highly reactive with water and will react quickly and exothermically with water when present. The process used to make the polyurethanes of the present invention, in which water is present, clearly leads to a polyurethane quite different from any polyurethane disclosed in Lipatova. As clear to one skilled in the art of isocyanate and polyurethane chemistry, the presence of water in the reaction mixture has substantial effects upon the chemical structure and physiochemical properties of the resultant composition as, for example, represented in scheme (1) above (wherein R is the residue of the isocyanate). As known to those skilled in the art of isocyanate and polyurethane chemistry, water acts as a chain extender, yielding a di-substituted urea - R-NH-C-NH-R- (the repeat unit enclosed within a rectangle in equation (1)) and gaseous carbon dioxide (CO<sub>2</sub>). The water reaction also substantially affects the morphology of the polyurethane through the release of the carbon dioxide (CO<sub>2</sub>) gas, which results in foaming and a porous.

foamed morphology. Although inherent to one skilled in the art, Applicants have amended independent claims 1 and 69 to set forth that the at least one multifunctional isocyanate compound is reacted with at least one bioactive agent having at least one reactive group  $-X$  which is a hydroxyl group ( $-OH$ ) or an amine group ( $-NH_2$ ) in a solution with a chain extender comprising water so that the multifunctional isocyanate compound reacts with the at least one bioactive agent and with the water to form a porous foam.

There is absolutely no disclosure or suggestion in Liptova of reacting isocyanate groups of at least one multifunctional isocyanate compound with at least one bioactive agent having at least one reactive group  $-X$  which is a hydroxyl group ( $-OH$ ) or an amine group ( $-NH_2$ ) in a solution with a chain extender comprising water so that the multifunctional isocyanate compound reacts with the at least one bioactive agent and with the water to form a porous foam. Urea repeat units as set forth in equation (1), which are present in the polyurethane compositions of the present invention, are absent from the polyurethanes of Liptova. Likewise, unlike the present invention, the polyurethanes of Liptova are not porous foams.

**Claims 1,3-11,15-16,18-20,22,25 and 69 are not anticipated under 35 U.S.C. 102(e) by Beckman et al. (US 7,264,823 B2)**

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Unlike the porous, foamed polyurethanes of the present invention, but like the polymers of Liptova et al., the adhesives of Beckman et al. are also be formed in the absence of water. See, for example, Examples 1 through 10. In that regard, the presence of water in the reactions of Beckman et al. would cause reaction of all isocyanate functionality in the compounds of Beckman et al., and thereby render the compounds of Beckman et al. ineffective as adhesives. Indeed, in distinguishing foamed polyurethanes in a declaration filed September 5, 2006 in Beckman et al. (available on the PAIR system of the United States Patent and Trademark Office), it was asserted that:

It is not an isocyanate-functional material, as the amended claims [of Beckman et al.] require. On the contrary, it lacks unreacted isocyanate groups altogether. This is a consequence of the reaction with water, which destroys any free isocyanate groups possibly remaining after the initial reaction between isocyanate and glycerol.

In the present invention, multifunction isocyanate compound are reacted with at least one bioactive agent in a solution with a chain extender comprising water so that the multifunctional

isocyanate compound reacts with the at least one bioactive agent and with the water (destroying any free isocyanate groups) to form a porous foam.

Compounds having isocyanate reactive functionalities such as polysaccharides, peptides, proteins, steroids etc. of Beckman et al. are reacted with excess multi-isocyanate compounds in Beckman et al. in the absence of water. Only after, such compounds of Beckman et al. are reacted with an excess of multi-isocyanate functionality to create the isocyanate functional adhesives of Beckman et al. are such adhesives exposed to a limited amount of moisture/water at a wound site. Beckman et al. does not disclose or suggest, reaction of multi-isocyanate compounds with a biologically active or bioactive agent in solution with a chain extender comprising water to form a porous, foamed polyurethane composition. The polyurethane compositions of the present invention have a substantially different chemical structure and morphology than the adhesives of Beckman et al.

**Claims 1,3-4,7-8,12,19,22,27-30,33 and 69 under are not anticipated under 35 U.S.C. 102(e) by Woodhouse et al. (US 6,221,997 B1)**

Once again, the presence of water in the formation of the polyurethanes of the present invention results in substantial changes in chemical composition and physiochemical characteristics as compared to the case in which a polyurethane is formed in the absence of water, as in the case of Woodhouse et al. As clear to one of ordinary skill in the art, and contrary to the Examiner's assertion, the product produced in Woodhouse is not the same as the presently claimed polyurethanes. Woodhouse et al. does not disclose or suggest, reaction of multi-isocyanate compounds with bioactive agents as set forth in the present claims in solution with a chain extender comprising water to form a porous, foamed polyurethane composition in which the bioactive agent is covalently attached.

Once again, the Examiner cannot ignore the claim limitation that the least one multifunctional isocyanate compound of the present invention is reacted with the at least one bioactive agent of the present invention in a solution with a chain extender comprising water so that the multifunctional isocyanate compound reacts with the at least one bioactive agent and with the water to form a porous foam. See, for example, Ex Parte Murphy and Burford, 217 USPQ 479,

481 (P.O. Bd. Appls. 1982) (“it is error to ignore specific limitations distinguishing over the cited reference”); In re Boe, 505 F.2d 1297, 184 USPQ 38 (CCPA).

### **Section 103**

**Claims 1,3-11,15-16,18-26 and 69 under are not unpatentable under 35 U.S.C. 103(a) over Zhang et al. (Biomaterials 21 (2000) 1247-1258) in view of Liptova et al. (Macromol. Symp. 152, 139-150 (2000)) or in view of Woodhouse et al. (US 6,221,997 B1)**

Zhang et al. discloses the reaction of glycerol with lysine diisocyanate in the absence of water to form a prepolymer. Water was then added to the prepolymer to induce crosslinking and foaming. On page 1248, Zhang et al. further indicates that the LDI-glycerol polymers thereof may allow incorporation of proteins of interest. As admitted by the Examiner, Zhang et al. is not enabling for covalent attachment of proteins within the polyurethane thereof. Zhang does not disclose even what is meant by “incorporation of proteins.” In that regard, native, unreacted proteins may be entrapped within the polymer matrix or within the pores of the polymer foam. To the contrary, in the present invention the at least one multifunctional isocyanate compound is reacted with the bioactive agent in solution with water so that the at least one bioactive agent is covalently incorporated within the resultant porous foam. There is no disclosure or suggestion in Zhang et al. of the reaction of a protein or any other bioactive agent in solution with water with a multi-isocyanate compound to form a polyurethane which is biodegradable to release the bioactive agent within a living organism.

Furthermore, for the reasons set forth above, one cannot combine the disclosure of Zhang et al. with the disclosure of Lipatova et al., Woodhouse et al. and/or any combination thereof to arrive at the present invention. Once again, neither Lipatova et al. nor Woodhouse et al. disclosure or suggest reaction of the least one multifunctional isocyanate compound with at least one bioactive agent in a solution with a chain extender comprising water as set forth in the present claims so that the multifunctional isocyanate compound reacts with the at least one bioactive agent and with the water to form a porous foam.

In view of the above amendments and remarks, Applicants respectfully requests that the Examiner, indicate the allowability of the Claims, and arrange for an official Notice of Allowance to be issued in due course.

Respectfully submitted,  
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